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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	Mirus.042.02	9890

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MIRUS CORPORATION  
505 SOUTH ROSA RD  
MADISON, WI 53719

EXAMINER
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DUNSTON, JENNIFER ANN

ART UNIT	PAPER NUMBER
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1636

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04/25/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/765,668	<b>Applicant(s)</b> ROZEMA ET AL.	
	<b>Examiner</b> Jennifer Dunston	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2007 and 17 January 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 5,7,8,12,16,17,21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 5,7,8,12,16,17,21 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/9/2007 has been entered.

Receipt is acknowledged of an amendment, filed 1/17/2008, in which claims 5, 7, 12 and 16 were amended, and claims 21 and 22 were newly amended. Currently, claims 5, 7-8, 12, 16-17 and 21-22 are pending.

Any rejections and objections not reiterated in this action have been withdrawn.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 7, 8, 12, 16, 17, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 5 recites the limitation "the compound" in line 9. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to replace the phrase "the compound" with the phrase "the polynucleotide."

Claims 7, 8 and 21 depend from claim 5 and thus are indefinite for the same reasons applied to claim 5.

Claim 12 recites the limitation "the compound" in line 9. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to replace the phrase "the compound" with the phrase "the polynucleotide."

Claims 16, 17 and 22 depend from claim 12 and thus are indefinite for the same reasons applied to claim 5.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5, 7, 8 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 7/26/2007 and has been extended to new claim 21.

Adams et al teach a method of delivery a polynucleotide to the cytoplasm of a cell, consisting of (i) forming a composition comprising a water soluble polymer such as styrene-maleic anhydride, divinylether-maleic acid or poly(maleic anhydride-co-vinyl ether) and a

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nucleic acid linked to the polymer via an ethylene group (a functional group), where the polymer is further modified by reacting with hydrophobic alcohols or amines, and (ii) administering the composition to a cell *in vitro* such that the cell endocytoses the polymer and nucleic acid (e.g. paragraphs [0037], [0057], [0081]-[0084], [0090]-[0093], [0162] and [0171]). Adams et al teach that the ethylene functional group is a reactive group (e.g., paragraph [0013]).

***Response to Arguments - 35 USC § 102***

With respect to the rejection of claims 5, 7, 8 and 21 under 35 U.S.C. 102(e) as being anticipated by Adams et al, Applicant's arguments filed 10/9/2007 have been fully considered but they are not persuasive.

The response asserts that the claims have been amended to obviate the rejection. Specifically, Applicant asserts that Adams does not teach the step of reacting hydrophobic amines or hydrophobic alcohols with anhydride monomers in the polymer. The response asserts that Adams et al only teach hydrophobic ethylene-containing groups or hydrophobic ethylene-reactive groups (at paragraphs 57-58 and paragraphs 48 and 70). Further, the response asserts that Adams et al do not teach direct hydrophobic modification of a styrene-maleic anhydride random copolymer or butyl vinyl ether-maleic anhydride alternating copolymer. Specifically, the response asserts that Adams et al teaches only activating a framework components (polymer) by means of an activating group and subsequently reacting with a group that includes a group that is reactive with the ethylene-derivatized nucleic acid (at paragraph 90) and teaches that activating the polymer consists of derivatizing the polymer with groups capable of undergoing reactions with nucleophiles or electrophiles (at paragraph 91).

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It is noted that Adams et al do teach activating a framework component (polymer) by means of an activating group reacted with a group that is reactive with the ethylene-derived nucleic acid, and these reactions include linkers that alter the hydrophobicity of the polymer (e.g., paragraphs [0050]-[0056]). However, Adams et al also specifically teach reacting the framework component (polymer) with hydrophobic alcohols or amines to alter the hydrophobicity, hydrophilicity, surface activity or conformation of the polymer (paragraph [0057]). At paragraph [0057], Adams et al state the following:

In another embodiment, the physicochemical characteristics (e.g., hydrophobicity, hydrophilicity, surface activity, conformation) of the polymer are altered by attaching a monovalent moiety which is different in composition than the constituents of the bulk polymer and **which does not bear a nucleic acid**. As used herein, "monovalent moiety" refers to organic molecules with only one reactive functional group. This functional group attaches the molecule to the polymer backbone. **"Monovalent moieties" are to be contrasted with the bifunctional linking groups described above.** Such monovalent groups are used to modify the hydrophilicity, hydrophobicity, binding characteristics, etc. of the polymer. Examples of groups useful for this purpose include **long chain alcohols, amines, fatty acids, fatty acid derivatives, poly(ethyleneglycol) monomethyl ethers, etc.** (Emphasis added.)

Thus, Adams et al specifically contrast the long chain alcohols and amines with the bifunctional linking groups discussed on page 4 of the reply. Adams et al teach reacting the polymer with the long chain alcohols and amines and teach that the polymer may be poly(styrene-maleic anhydride) (e.g., paragraph [0083]). Thus, the teachings of Adams et al meet each of the limitations of the rejected claims. It is noted that claims 12, 16, 17 and 22, which require butyl vinyl ether-maleic anhydride alternating copolymer were not included in the Adams et al rejection under 35 U.S.C. 102(e).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 12, 16, 17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference) in view of Tonge et al (US Patent No. 6,436,905, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 7/26/2007 and has been extended to new claim 22.

The teachings of Adams et al are described above and applied as before.

Adams et al do not specifically teach poly(maleic anhydride-co-vinyl ether) where the vinyl ether is butyl vinyl ether.

Tonge et al teach a composition comprising a synthetic amphipathic polymer, including both hydrophobic groups and anionic hydrophilic groups and acting as a lipid-solubilizing agent (e.g. column 3, lines 49-52). Tonge et al teach that especially suitable polymers may be formed as alternating copolymers of maleic acid (or the anhydride thereof) with styrene, indene or a C<sub>1-4</sub> alkyl, e.g. methyl substituted styrene or indene, or with propyl (or isopropyl) or butyl vinyl ether

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(e.g. column 6, lines 27-31, 60-63). Tonge et al disclose examples of suitable polymers, including Poly(maleic anhydride-styrene) (a random copolymer), Poly(maleic anhydride-propyl vinyl ether), and Poly(maleic anhydride-butyl vinyl ether) (e.g. column 6, lines 60-63). Tonge et al teach the use of the polymers to administer drugs or DNA or RNA to cells to facilitate the uptake of the therapeutic agent into target cells (e.g. column 1, lines 31-45; column 12, line 40 to column 13, line10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a nucleic acid to a cell using a poly(maleic anhydride-co-vinyl ether)-based composition to include butyl vinyl ether as the vinyl ether, which is taught by Tonge et al, because Adams et al and Tonge et al teach it is within the ordinary skill in the art to use poly(maleic anhydride-co-vinyl ether)-based compositions for the delivery of nucleic acid to a cell.

One would have been motivated to make such a modification in order to receive the expected benefit of defining the complete structure of the poly(maleic anhydride-co-vinyl ether) with a vinyl ether suitable for the delivery of nucleic acid as taught by Tonge et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### ***Response to Arguments - 35 USC § 103***

The rejection of claims 5, 7, 8, 12, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Tonge et al in view of Maeda et al has been withdrawn in view of Applicant's



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amendment to the claims in the reply filed 1/17/2008. The claims have been amended to a method “consisting of” the recited steps. Tonge et al teach the step of adding a lipid, which is not encompassed by the instant claims.

With respect to the rejection of claims 12, 16, 17 and 22 under 35 U.S.C. 103(a) as being unpatentable over Adams et al in view of Tonge et al, Applicant's arguments filed 10/9/2007 have been fully considered but they are not persuasive.

The response asserts that the amendments to overcome the rejection under 35 U.S.C. 102(e) are also sufficient to overcome the rejection under 35 U.S.C. 103(a). This is not persuasive for the reasons set forth above. As noted above, Adams et al do not specifically teach the method where the vinyl ether of the polymer is butyl vinyl ether. Tonge et al remedies this deficiency. Thus, the combined teachings of Adams et al and Tonge et al meet each of the limitations of the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

#### ***Citation of Relevant Art***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Salamone, J.C. “Maleimide Copolymers (N-Substituted)” in Polymeric Materials Encyclopedia. CRC Press, pages 3996-4013, 1996.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.  
Examiner  
Art Unit 1636

/JD/

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Primary Examiner, Art Unit 1636